Hyperekplexia as the presenting symptom of Creutzfeldt-Jakob disease

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Practical Implications

Creutzfeldt-Jakob disease should be considered in the differential diagnosis of hyperekplexia.

Video

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We describe a patient with hyperekplexia as the initial presenting symptom in sporadic Creutzfeldt-Jakob disease (CJD). We also demonstrate the utility of the sensitive and highly specific new prion protein amplification assay, real-time quaking-induced conversion (RT-QUIC), which amplifies and detects misfolded β -sheet-rich conformers of the prion protein (PrP^{sc}), in expediting a confident clinical diagnosis of CJD in an atypical case.

Case report

A 73-year-old man presented with 4 months of an exaggerated startle response (hyperekplexia) occasionally but not exclusively associated with myoclonus and without cognitive decline at onset (video at Neurology.org/cp). The detailed case report is presented in appendix e-1.

Blood tests revealed mildly low complement and a positive lupus anticoagulant. CSF twice revealed normal biochemistry and no cells or oligoclonal bands. CSF 14-3-3 protein was not detected by Western blot. Tremor studies revealed an inconsistent order of myoclonic recruitment and entrainment of tremor to externally paced hand tapping, which alone suggested a psychogenic movement disorder. An EEG demonstrated bifrontal spikes that sometimes

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preceded clinical myoclonus (figure, A). SPECT imaging demonstrated widespread discrete areas of hypoperfusion involving the cerebral cortex with a focal area of right frontal hyperperfusion (figure, B and C). MRI revealed focal linear cortical T2 hyperintensities (figure, D–G). A formal cerebral angiogram was normal.

Figure Results of EEG, radiology, and histopathologic investigations

(A) EEG demonstrated intermittent bifrontal and right frontal spikes that often preceded a myoclonic jerk. There was no EEG evidence of a seizure or any periodic lateralized epileptiform discharges. (B–C) SPECT imaging demonstrated widespread discrete perfusion abnormalities involving the cerebral cortex and sparing the subcortical regions, with a focal area of increased activity in the right frontal lobe representing a region of hyperperfusion. This right frontal hot spot (arrow) is visible on both coronal (B) and axial (C) images. (D–G) 3T MRI coronal and axial reformats from a 3D fluid-attenuated inversion recovery sequence acquired in the sagittal plane revealed small focal ribbons of cortical T2 hyperintensity (coronal, D; axial, F) with associated diffusion restriction (arrow) (coronal, E; axial, G reformats from a high-resolution diffusion-weighted imaging sequence acquired in the axial plane with a slice thickness of 1.8 mm and with B0 and B1000); corresponding apparent diffusion coefficient map changes were present (data not shown). (H) Predominantly microvacuolar spongiform change was present in the cortex, including perineuronal and perivascular vacuolation, with associated mild neuronal loss and reactive gliosis (hematoxylin & eosin [H&E] stain, magnification 630×). (I) 3F4 immunohistochemistry of the cortex revealed a synaptic staining pattern with globular plaque-like immunoreactive deposits admixed (3F4 immunohistochemistry, magnification 400×). (J) The cerebellar vermis and lateral hemispheres showed mild macrovacuolar spongiform change in the molecular layer, Bergmann gliosis (arrow) with Purkinje cell drop out, numerous torpedo-like eosinophilic swellings (asterisk), and many Kuru-type plaques in the molecular and granular layers (inset) (H&E stain, magnification 630×; inset 1200×). (K) Immunostaining for prion protein in the cerebellar vermis showed intense immunoreactivity of Kuru plaques, small clusters of plaques, and fine synaptic staining mostly restricted to the granular layer, with occasional plaques seen in the white matter and molecular layer (3F4 immunohistochemistry, magnification 630×).

Differential diagnoses at this stage included CJD, cerebral vasculitis, and progressive encephalopathy with rigidity and myoclonus. Testing of CSF using the RT-QUIC assay was positive, strongly supporting a diagnosis of CJD.¹

The patient declined, with gait and cognitive impairment plus behavioral changes, and died 13 months following symptom onset. Postmortem brain analysis confirmed CJD with histopathologic features of microvacuolation (spongiform changes) and Kuru-type plaques (figure, H–K). Sequencing of the entire PrP gene (*PRNP*) open reading frame was normal, confirming sporadic CJD with heterozygosity for methionine/valine at codon 129. Glycotyping revealed type 3 PrP^{Sc}.²

DISCUSSION

Sporadic CJD is a prion disease consequent to accumulation of misfolded pathogenic prion protein in the brain.³ It typically presents with cognitive decline. Clinical heterogeneity correlates with the molecular subtype, depicted by the combination of the methionine (M) or valine (V) polymorphism at codon 129 of *PRNP* and PrP^{Sc} glycoform demonstrated through Western blot analysis of brain homogenates. Postmortem histopathology in this case was unusual in that there were Kuru-type plaques in the cerebellum, consistent with what is reported for MV3,⁴ with immunostaining for PrP also showing PrP-positive plaques in the cortex and basal ganglia.

This patient's initial symptom was an exaggerated startle response (hyperekplexia). A startle reflex is a bilaterally synchronous shocklike set of movements.⁵ A number of mutations in the glycine receptor gene and other postsynaptic proteins are associated with inherited hyperekplexia.⁵ Acquired forms may be secondary to brainstem or extensive cerebral damage or glycine receptor antibodies.⁵ Although myoclonus is an established clinical feature in CJD, hyperekplexia as the initial symptom of sporadic CJD is unique.

This case exemplifies the difficulty clinicians may face in the diagnosis of sporadic CJD. Our case was atypical for sporadic CJD because the patient presented with hyperekplexia, initially preserved cognition, a longer disease course, and the absence of CSF 14-3-3 protein.

Although CSF 14-3-3 protein detection is a useful confirmatory test for sporadic CJD, it is a nonspecific marker of neuronal damage, and both its sensitivity and specificity can be suboptimal. CSF tau levels have been shown to have a higher specificity for the diagnosis of CJD than 14-3-3³; however, these results were not available for our patient. In 2011, Atarashi et al.¹ described a new amplification assay, RT-QUIC, which allowed for the ultrasensitive detection of PrP^{Sc} in CSF samples with greater than 80% sensitivity and 100% specificity, thus permitting an early, rapid, and highly specific antemortem diagnostic investigation. Further independent studies have demonstrated a sensitivity of 87% or more in sporadic CJD with retained high specificity.⁶ The RT-QUIC assay has also been identified as being more sensitive for the detection of genetic prion disease than biomarkers such as 14-3-3 or tau protein.⁷

This case is unique because it highlights hyperekplexia as a possible presenting symptom of sporadic CJD. It also demonstrates the utility of the highly sensitive and specific RT-QUIC assay in supporting an antemortem clinical diagnosis of CJD in a case where immunologic findings on blood tests may otherwise have suggested invasive investigation and treatment trials for possible vasculitis, a recognized differential diagnosis in CJD.

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